IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
David FIKSTAD et al.	)	Group Art Unit: 1618
Application No.: 09/871,318	)	Examiner: Micah Paul Young
Filed: May 31, 2001	)	Confirmation No.: 1207
For: TRANSDERMAL DELIVERY OF LASOFOXIFENE	)	

DECLARATION UNDER 37 CFR.1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Andrew Coop, declare as follows:

1. I am a permanent resident of the United States, and reside at 9462 Ridgeview Drive, Columbia, MD 21046

2. I am currently a Professor and Chair of the Department of Pharmaceutical Sciences at the University of Maryland School of Pharmacy. I have been employed as Chair of the Department for 15 months, and oversee 23 faculty members with interests from molecular biology, to pharmacology, to chemistry, to pharmaceutics and drug delivery, to clinical sciences. I have been employed in the faculty position for ten years. In this position, I have overseen a medicinal chemistry program utilizing modern drug design techniques and novel organic methodology in the design and synthesis of ligands targeted at biological systems involved in drugs of abuse and cancer. The most relevant work to

this declaration includes my studies on opioids, Gamma-hydroxybutyrate, and sigma receptor antagonists. Prior to my current employment, I was a Fogarty Fellow in the Laboratory of Medicinal Chemistry at the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health. In this position, I focused my work on analogs of naltrindole, and new methodology.

3. I received my Bachelor's and Master's degrees from St. Catherine's College, at the University of Oxford. While obtaining these degrees, I performed research on organo-lean and tin compounds.

4. I received my Ph.D. in Chemistry from the School of Chemistry at the University of Bristol where I focused my research on ring constrained analogues of buprenorphine.

5. As part of this opinion, I would consider a person who is skilled in the field of the invention to be one having a doctoral degree in the fields of chemistry, pharmaceutics, pharmacology, medicinal chemistry or a related discipline.

6. I have reviewed the Fikstad et al. application (US 2002/0037311) and claims 14, 18, 19 and 25-27 and have been asked whether the combination of Ebert et al. (US 5,662,925), Cormier et al. (US 6,203,817) and Ke et al. (US 6,323,232) would result in these claims being obvious to a person who is skilled in the field.

7. My answer to this request, in short, is no, the combination of Ebert et al. (US 5,662,925), Cormier et al. (US 6,203,817) and Ke et al. (US 6,323,232) would not result in claims 14, 18, 19 and 25-27 being obvious to a person who is skilled in the field.

8. My opinion in this regard is based on the fact that the chemical properties of compounds listed in these publications ultimately dictate how they may be formulated. I also, believe that the combination of these publications relies on the false presumption that drugs may

be interchanged in different formulations based solely on their pharmacological classification.

9. To demonstrate why I believe that these compounds may not be interchange requires a comparison of lasofoxifene to tamoxifen, droloxifene, idoxifene, raloxifene HCl and tamoxifen citrate. In regard to the structure of lasofoxifene, I define this compound as possessing three aromatic rings that are constrained through a 6–membered restraining ring. As a result, the lasofoxifene structure is very different from all of the other drugs listed above which do not have a constraining ring, with the exception of Raloxifene that has a very different 5-membered sulfur-containing planar ring. The effect of these differences is that the constraint of these rings forces a different conformation to the non-constrained compounds, and will lead to significantly different physical properties compared to all other compounds listed. Each of these properties would, in turn, have an effect on the manner in which it is formulated.

10. In addition to the basic structure of the compounds differing, they all also possess differing functional groups from each other. For example, the compounds contain piperidine, pyrolidine, thiophene, phenol, carboxylic acid and halogenated aromatic groups. These functional groups affect properties such as the stability of the active ingredient, stability of the adjuvant in combination with the active ingredient, phase distribution within a matrix, release from the matrix, pH and bioavailability. All of which must be accounted for in formulating a transdermal formulation.

11. In sum, each of these differences in chemical make up of these compounds introduces a layer of unpredictability to the use of these compounds, especially with regard to formulations. And this unpredictability would then transcend to the unpredictability of

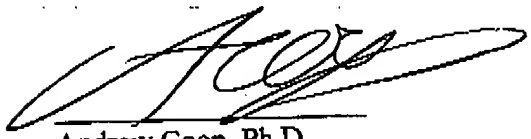
the kinetics by which a drug passes out of the matrix and into the patient receiving therapy.

12. In addition to the layers of unpredictability with regard to the chemical make-up of compounds, there is also unpredictability in the transdermal device in itself. For example, since each of the compounds listed in the Cormier, Ke and Ebert publication possess certain qualities with regard to solubility, pH etc., these would require modifications of the device that would require the differences in how each drug would interact with the other compounds or adjuvants in the formulation as well as the phase distribution in the matrix and the release form the matrix to be accounted for. As a result, the material make-up of the device would have to be varied to prevent degradation of the drug, increase stability of the drug, and provide bioavailability of the drug to the patient. All of which are unpredictable factors that may or may not lend a drug to being formulated for transdermal delivery.

13. In view of these unpredictable considerations in formulating a transdermal device for the delivery of lasofoxifene, I believe that one who is skilled in the field, would not recognize that the topical administration of an aqueous solution of lasofoxifene as described in Ke et al. would in any way predictably dictate that the same concept would translate to the transdermal delivery of lasofoxifene using the device and methods as set forth in claims 14, 18, 19, and 25-27. In fact, I believe that the topical administration of an aqueous solution of any drug would not be suggestive of whether that drug could be incorporated into a transdermal delivery device because many unpredictable factors must be taken into account not only with the drug, but also with the device itself as discussed above.

14. Therefore, it is my opinion that one who is skilled in the field would not find the transdermal device and methods for delivering lasofoxifene as set forth in claims 14, 18, 19 and 25-27 to be obvious in view of the combination of the Cormier, Ke and Ebert publications. This is because several assumptions must be made based on the unpredictable components would lead one who is skilled in the field to conclude that the combination of lasofoxifene in a transdermal drug delivery device and related methods of treatment would not be a predictable based on their established functions.

15. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code.



Andrew Coop, Ph.D.

October 27, 2008
Date